acid probes that Applicants contemplated probes of at least 8 nucleotides. The Examiner's attention is specifically directed to page 20, lines 19-21, which states

> "This number of nucleotides is usually about the minimal length required fro a successful probe that would hybridize specifically with an HPC2-encoding sequence. In this context oligomers of as low as 8 nucleotides, more generally 8-17 nucleotides can be used for probes, especially in connection with chip technology."

Thus, it is clear that Applicants contemplated probes of at least 8 nucleotides.

In addition, there can be no question in the mind of a person of ordinary skill in the art of nucleic acid probes that Applicants contemplated probes based on the *HPC2* gene. The Examiner's attention is specifically directed to page 23, line 29 - page 24, line 1, which states

> Probes for HPC2 alleles may be derived from the sequences of the HPC2 region, its cDNA, functionally equivalent sequences, or the complements thereof. The probes may be of any suitable length, which span all or a portion of the HPC2 region, and which allow specific hybridization to the HPC2 region. If the target sequence contains a sequence identical to that of the probe, the probes may be short, e.g., in the range of about 8-30 base pairs, since the hybrid will be relatively stable under even highly stringent conditions.

Furthermore the specification at page 24 lines, 19-31 states,

> Portions of the polynucleotide sequence having at least about eight nucleotides, usually at least about 15 nucleotides, and fewer than about 9 kb, usually fewer than about 1.0 kb, from a polynucleotide sequence encoding HPC2 are preferred as probes. This definition therefore includes probes of sizes 8 nucleotides through 9000 nucleotides. Thus, this definition includes probes of 8, 12, 15, 20, 25, 40, 60, 80, 100, 200, 300, 400 or 500 nucleotides or probes having any number of nucleotides within these ranges of values (e.g., 9, 10, 11, 16, 23, 30, 38, 50, 72, 121, etc., nucleotides), or probes having more than 500 nucleotides. The probes may also be used to determine whether mRNA encoding HPC2 is present in a cell or tissue. The present invention includes all novel probes having at least 8 nucleotides derived from any of SEQ ID NOs:1 or 3-28 its complement or functionally equivalent nucleic acid sequences. The present invention does not include probes which exist in the prior art. That is, the present invention includes all probes having at least 8 nucleotides derived from any of SEQ ID NOs:1 or 3-28 with the proviso that they do not include probes existing in the prior art.

Thus, it is clear that Applicants contemplated probes of at least 8 nucleotides of the *HPC2* gene.

The Examiner contends that Applicants have disclosed only the structural features of one species, the polynucleotide of SEQ ID NO:1 and the polypeptide of SEQ ID NO:2 encoded by SEQ ID NO:1. It is submitted that the Examiner is incorrect. Applicants have disclosed structural features of the probes, i.e., at least 8 contiguous nucleotides of the nucleic acid of SEQ ID NO:1 or of a nucleic acid encoding the protein of SEQ ID NO:2. Since SEQ ID NO:1 and SEQ ID NO:2 have structural features, it is evident that a nucleic acid probe comprising at least 8 nucleotides of this sequence also has a specified structural feature.

The Examine is reminded that the test is whether the specification reasonably conveys to a skilled artisan in the relevant art, i.e., DNA probes, that Applicants were in possession of the claimed invention at the time of application filing date. A skilled artisan in the probe art knows that probes are short oligomers of a specified target sequence, such as *HPC2* described in the present application. The skilled artisan further knows that probes are derived from a target sequence which specifically hybridize to the target sequence. Since the specification states that the invention is directed to probes of at least 8 nucleotides which are specific to *HPC2*, it is evident that the specification "reasonably conveys" to the skilled artisan that Applicants were in possession of the claimed invention, i.e., the probes of claims 10 and 64-66.

Claims 25 and 78 are directed to a pair of single-stranded primers for determining of a nucleotide sequence of a wild-type *HPC2* gene (25) or of a specified *HPC2* gene variant (78) in an amplification reaction. The primers are 13 or more nucleotides long and are identical to or complementary to SEQ ID NO:1 or SEQ ID NO:1 with the specified variant. Primers are described at page 13, line 21 - page 14, line 3 and page 24, line 32- page 25, line 10. The number of nucleotides contemplated for such primers are described at page 24, line 32- page 25, line 10. The specification at page 24, lines 32-33 states

> Similar considerations and nucleotide lengths [as with probes] are also applicable to primers which may be used for the amplification of all or part of the HPC2 gene.

Thus, all of the references to the specification made above are also applicable to demonstrating that the specification fully discloses the claimed invention.

The specification describes the primers at page 13, lines 21-28 which states

> The primer pairs of the present invention are useful for determination of the nucleotide sequence of a particular HPC2 allele using PCR. The pairs of single-stranded DNA primers can be annealed to sequences within or surrounding the HPC2 gene on chromosome 17 in order to prime amplifying DNA synthesis of the HPC2 gene itself. A complete set of these primers allows synthesis of all of the nucleotides of the HPC2 gene coding sequences, i.e., the exons. The set of primers preferably allows synthesis of both intron and exon sequences. Allele-specific primers can also be used. Such primers anneal only to particular HPC2 mutant alleles, and thus will only amplify a product in the presence of the mutant allele as a template.

Thus, it is clear that Applicants contemplated primers useful for the amplification of *HPC2* gene or *HPC2* mutant alleles.

A skilled artisan in the primer/amplification art knows that primers are short oligomers of a specified target sequence, such as *HPC2* described in the present application. The skilled artisan further knows that primers are derived from a target sequence which specifically hybridize to the target sequence. Since the specification states that the invention is directed to primers of 13 or more nucleotides which are specific for amplification of *HPC2*, it is evident that the specification "reasonably conveys" to the skilled artisan that Applicants were in possession of the claimed invention, i.e., the primers of claims 25 and 78.

In view of these remarks, it is submitted that claims 10, 25, 64-66 and 78 are described in the specification as required by 35 USC §112, first paragraph. Withdrawal of this rejection is requested.

Claims 10, 25, 64-66 and 78 have been rejected under 35 USC §112, first paragraph for lack of enablement. In making this rejection, the Examiner relies on considerations with respect to proteins, subject matter which is not being claimed in the rejected claims. In addition, the Examiner contends that the disclosure of one HPC2 polynucleotide encoding a corresponding polypeptide is insufficient support for claims which encompass any and all polynucleotides and fragments. Applicants submit that the Examiner is in error in this rejection.

First, the Examiner's contention with respect to the alleged insufficient support for the claimed invention is not a proper reason for rejection of claims for lack of enablement. While the scope to the claims is one of the Wands factors, the support in the specification is not and is not an issue for enablement.

Second, the Examiner's analysis of the predictability of the claimed invention is in error. Applicants are not claiming proteins or variants of proteins and are not claiming polynucleotides which encode variant proteins. Instead the claims are directed to nucleic acid probes (claims 10 and 64-66) or to oligonucleotide primers (claims 25 and 78). Thus, any statements with respect to proteins and effects of changes in protein sequence or structure is irrelevant to probes or primers. The probes or primers of the claimed invention may detect or be used to amplify wild-type *HPC2* or specified *HPC2* variants. As is well known to a skilled artisan in the relevant art, probes are used to detect the presence of a target sequence and primers are used for the amplification of a desired target sequence. Further, it is well known to a skilled artisan that probes and primers are based on the nucleotide sequence of a target sequence. Thus, probes, primers and their use for detecting nucleic acids or for amplification of nucleic acids is predictable.

The test for "enablement" is whether at the time the application was filed, one reasonably skilled in the art could make and use the claimed invention, from the disclosure in the specification coupled with information known in the art, without undue experimentation. *See*, e.g., *In re Wright*, 27 U.S.P.Q.2d 1510, 1514 (Fed. Cir. 1993); *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001, 1006 (Fed. Cir. 1991); *See also Genentech, Inc. v. Novo Nordisk*, 42 U.S.P.Q. 2d 1001, 100 (Fed. Cir. 1997) ("[R]easonable detail" must be provided in the specification "to enable members of the public to understand and carry out the invention.") Applicants submit that the emphasis is on the claimed invention, not on all of the subject matter which may be disclosed in the specification. Thus, at the time the present application was filed (as well as at the time of filing of the parent applications), the skilled artisan would have been able to make and use the claimed invention, using the teachings in the specification coupled with information known in the art, without an undue amount of experimentation. Specifically, an application of the Wands factors clearly demonstrate that the specification is fully enabling for the claimed subject matter.

The Quantity of Experimentation Necessary

The present claims are directed to probes and primers. The probes comprise at least 8 contiguous nucleotides of a nucleic acid encoding a protein of SEQ ID NO:2 or a specified variant. The primers comprise 13 or more nucleotides and are identical or complementary to SEQ ID NO:1 or a specified variant. Applicants submit that there is no experimentation necessary to make probes

or primers and to use them for detecting nucleic acids or for amplifying nucleic acids. It is incumbent on the Examiner to provide valid scientific reasons or evidence to sustain an enablement rejection. *In re Marocchi*, 169 USPQ 367 (CCPA 1971). The Examiner has not provided any valid scientific evidence or reasons with respect to making and using probes or primers.

The Amount of Guidance Provided in the Specification

The present specification provides sufficient guidance to a person of ordinary skill in the art to practice the claimed invention. The specification clearly describes the target sequence for the probes and primers. The specification further provides guidance for techniques for using probes and primers for their specified purposes, all of which were well known to a skilled artisan at the time of filing the present application. Thus, the specification provides guidance to a skilled artisan for the breadth of the claimed subject matter.

The Presence or Absence of Working Examples

The specification provides working examples for the use of primers for amplifying genes. Although the application does not provide working examples of the use of probes, such use was well known at the time of filing the application as evidenced by the extensive discussion in the specification.

Nature of the Invention

The present invention is in the area of probes and primers for detecting or amplifying target sequences. Most aspects of this technology is completely predictable as evidenced by numerous texts and literature articles on DNA probes and amplification techniques. For example, a skilled artisan can predict with reasonable certainty that a probe can be used to detect a target sequence and that a primer can be used to amplify a desired target sequence. Thus, for the factors of the present invention, the degree of unpredictability is low.

The State of the Prior Art

As discussed in great detail above, the state of the art with respect to probes and primers and their use is very broad. In this context, the state of the prior art with respect to probes, primers and their use is not limited in any respect. In addition, techniques for preparing such probes and primers are not limited in any respect. Thus, it is submitted that applications of these techniques to the claimed method are not limited in any respect.

The Relative Skill in the Art

The relative skill in the art is low. Undergraduate students today routinely perform experiments in utilizing probes and primers for detecting or amplifying target sequences. These students can readily prepare probes and primers when provided with sufficient information as to the target sequence, such as the *HPC2* gene disclosed in the present specification. Numerous texts and literature articles on DNA probes and amplification techniques are available in the art which provide all of the necessary instructions for making and using probes and primers. The Examiner is no doubt well aware of Sambrook et al. (*Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989) and Ausebel et al. (*Current Protocols in Molecular Biology*, J. Wiley and Sons, N.Y., 1992, and periodic updates) and numerous volumes of *Methods in Enzymology*. These references were well known to persons of skill in the art at the time of the invention. Thus, a person of skill in the art would at least know the basics of probe and primer technology, which would enable him to practice the claimed invention on the basis of the present disclosure.

The Breadth of Scope of the Claims

The Examiner contends that the claims are broad on the basis of several factors. Applicants agree that the claims may be broad, but this factor alone is insufficient to render the claims enabled by the specification. The claims are directed to probes and primers having specified sequence. They are not directed to nucleic acids which encode a protein as argued by the Examiner.

Thus, as demonstrated above, the probes and primers and their use is predictable, significant guidance has been provided by the specification, working examples demonstrating the invention have been provided, the state of the art is well developed and the level of skill in the art is not high. Thus, a proper application of the *Wands* factors demonstrates that the specification is fully enabling for the claimed subject matter and that no undue experimentation is necessary to practice the claimed invention. For all of the above reasons, it is submitted that the specification is fully enabling to a person of ordinary skill in the art.

In view of these remarks, it is submitted that claims 10, 25, 64-66 and 78 are fully enabled by the specification as required by 35 USC §112, first paragraph. Withdrawal of this rejection is requested.

Applicants acknowledge the Examiner's indication that claims 1-3, 11-15, 61-63 and 67-77 are allowable.

In view of the above remarks, it is believed that the present application meets the requirements of the patent statutes and is patentable over the prior art. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned in order to expedite the prosecution of this application.

RESPECTFULLY SUBMITTED,					
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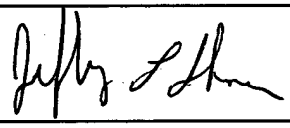
SIGNATURE				*DATE*	2 April 2002
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